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**PATENT
1718-0214P**

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: **HARMENBERG, Johan G. et al.** Conf.: **2442**
Appl. No.: **10/771,259** Group: **1614**
Filed: **February 2, 2004** Examiner: **KRASS, F.**
For: **PHARMACEUTICAL COMBINATION**

DECLARATION SUBMITTED UNDER 37 C.F.R. § 1.132

Honorable Commissioner
Of Patents and Trademarks
PO Box 1450
Alexandria, VA 22313-1450

July 2, 2005

Sir:

I, Dr. Spotswood Spruance of the Division of Infectious Diseases and Division of Dermatology, University of Utah Medical School, United States do hereby declare the following:

I have attached a copy of my curriculum vitae to this Declaration.

I am Professor in the Divisions of Infectious Disease and Dermatology and have worked in the research and clinical treatment of viral infections for 35 years.

I am familiar with the above referenced patent application (referred to below as the Harmenberg application), as well as the clinical management of herpes viral infections.

I have read and understand the subject matter of the Office Action of March 4, 2005, including the prior art references cited therein and the claims under review/examination.

The following comments are offered in support of the patentability of the Harmenburg invention.

Before addressing the Examiner's statements regarding the Levin (USP 5,656,301), Smith (USP 4,902,678) and Underwood (USP 3,317,384) references I would like to make the following comments.

First, each infectious disease has several components. For example, a dermal herpes simplex virus (HSV) infection has the following main components: (1) death of cells, (2) inflammation, (3) wound healing and (4) pain. Many infectious diseases have some symptoms or components in common, such as pain, redness and swelling.

Second, treatment of the disease is targeted to the component of the disease having the greatest impact on the patient. That is, the disease components are prioritized as to the discomfort/danger that they cause the patient and the symptom or component with the highest priority/discomfort/danger is targeted for treatment. In many cases, once the highest priority component has been treated the body is capable of alleviating the other components of the disease without further intervention.

Third, it is only when the treatment is no longer effective that treatment directed towards the second highest priority will begin. That is, the medical community must agree that the ceiling of treatment benefit has been reached before another drug or treatment will be added to the treatment regime and which targets the second component of the disease.

Fourth, because of the many ethical concerns involving treatment of human patients, it is only in rare cases that the procedure described above is not followed. Here, an example would be a patient who was unresponsive to the accepted treatment and whose life was endangered. But in this case, while an experimental treatment might be tried, the experimental treatment would offer little more than simple hope.

Fifth and lastly, the use of steroids for the treatment of infectious disease has been advanced cautiously. For example, it was not until about 30-40 years ago that steroids were first used, in this case for the treatment of tuberculous meningitis, because anti-tuberculosis antibiotic treatments were unsatisfactory. From that time until 1995, steroids had only been accepted as standard treatment for two other infectious diseases —Pneumocystis carinii and fungal infection of the toes. This cautious advance has predominantly been in cases where the inflammatory effects have been equal to or greater than the damage done by the pathogen. In addition, until relatively recently it was feared that glucocorticoids stimulated viral replication in HSV infections, exacerbating the disease.

Levin

The Examiner states that it would be obvious to combine parts of two compositions, each of which is useful for the same purpose, to obtain a third composition also useful for the same purpose is obvious. In particular the Examiner refers to topical application of 0.5% acyclovir + LYCD to a HSV infection and topical application of 0.5% hydrocortisone + LYCD to a patient suffering from "shingles." This statement implies that the Examiner considers HSV and "shingles" (resulting from a previous herpes zoster infection) to be the same disease. This is incorrect. While these two diseases share many symptoms or components, the symptoms or components are prioritized very differently for the two diseases, with inflammation and pain commanding the top priorities for shingles. This contrasts markedly to the prioritization of symptoms for a dermal HSV infection (see general remarks above).

Levin himself describes "shingles" as an acute inflammatory disease (see column 11) rather than a viral disease. Shingles (herpes zoster) largely results from the immune response to reactivation of the chicken pox virus (varicella-zoster virus) that lays dormant in nerve cells near the spine and brain. The immune response causes inflammation of the skin and is thought to be the cause of chronic pain (post-herpetic neuralgia) which is present in about 10-20% of patients long after the skin lesions are gone.

Example 32 in the Levin reference discusses patients who have had shingles symptoms for some time and for whom the conventional treatment failed. So the use of an alternative treatment, in this case hydrocortisone and LYCD, was tried. This situation is most similar to my fourth remark above, where deviation from the accepted standard treatment method happens only when the standard treatment fails and the patient's life is endangered. Typically, in this situation there would be no more than a 50-50 expectation of successful treatment.

So to summarize, the Examiner is **incorrect** that the separate applications of acyclovir and hydrocortisone are for the **same purpose**; in fact they were **administered for different purposes**. Acyclovir, an antiviral, was administered to kill virus in a dermal HSV infection while hydrocortisone was administered to reduce inflammation and pain in a shingles patient. Furthermore, one of ordinary skill in the art **would not have been motivated to combine** these two compounds to treat a mere cold sore because the risks to the patient of undertaking an unproved treatment would be too great. Yet even if one did, based on the Levin reference the skilled artisan **would not have had a reasonable expectation of success** in treatment because the hydrocortisone + LYCD was administered to patients who had failed to respond to standard treatment.

Smith and Underwood

The Examiner states that it is well-known to use a glucocorticoid to decrease side effects associated with topical antiviral nucleosides when treating herpes infections and refers to column 1, lines 32-39 of the Underwood reference. He concludes that one skilled in the art would have been motivated to improve the therapeutic efficacy of herpes treatment by reducing the side effects of an antiviral by incorporating a glucocorticoid into the antiviral combinations described by Smith.

Unfortunately, the Examiner has misunderstood Underwood's comments in column 1. Underwood discusses treatment of herpetic conditions in the eyes. Steroids have been the primary treatment for eye infections for a long while because the danger of inflammation in ocular disease has been well recognized. Unlike a dermal HSV infection, the components of ocular herpes infections are prioritized as follows: (1)

inflammation, (2) cell death, (3) wound healing and (4) pain. This is due, in part, to the differences between ocular and dermal tissues. That is, eye tissues affected by herpes infections are not actively growing as are dermal tissues. In any event, steroids and glucocorticoids are the drugs of choice to alleviate the highest priority symptom/disease component.

Underwood's comments in column 1 do not discuss the side effects associated with topical antiviral nucleosides but instead discusses the **side effects associated with glucocorticoids**. For example, on lines 24-25 Underwood states "Secondary encephalitis is a hazard of such application and can result in death." Also, on lines 29-33 Underwood states "Moreover, glucocorticoids are known to mask progress of herpetic conditions in the eye whereby infection progresses despite apparent improvement." This particular statement accurately reflects the concerns about use of steroids for treatment of HSV infections that have existed until recently, as discussed above. Underwood's discussion of the side effects associated with steroid use also indicates that the ceiling of treatment benefit for use of steroids had likely been reached and provided incentive to try to alleviate the next component of the disease.

On the other hand, steroids have never been recognized as the primary treatment for dermal infections. Antivirals have always been the primary treatment and no particularly dangerous side effects have been noted. As a consequence, and because of the constant improvement of antiviral compounds reaching the marketplace, there was **no motivation** to look outside of the antivirals for treatment improvement. In addition, Underwood's comments regarding the hazards associated with use of glucocorticoids for treatment of herpetic conditions **teach away from** making an antiviral-glucocorticoid combination.

In fact, it was not until the Harmenburg animal model was developed which accurately simulated the role and effect of the immune system in recurrent dermal HSV infections that it began to become apparent that the ceiling of treatment benefit had been reached for use of antivirals alone. The classical animal models, such as the monkey and rabbit models used by Underwood, relied on the response of a *primary* infection to a drug combination. Here, the immune system has not yet been "primed" and the ability of a drug to alleviate symptoms is more exaggerated. The extent of this

exaggeration was not truly appreciated until the animal model system developed by and used in the Harmenburt patent became widely available. The reliance on the classical model systems led people to think that the increases in potency of new antivirals would continue to positively effect treatment.

Not only would the skilled artisan have not been motivated to look outside of antivirals for treatment, but the lack of any data presented in the paper with respect to treatment of dermal infections would have further deterred one from making an antiviral-glucocorticoid combination. **At best**, the information presented in the Underwood reference would have made it **obvious to try** a combination of an antiviral and glucocorticoid. But it is my understanding that this is **not the legal standard** for obviousness, for example, one could not have had a reasonable expectation of success.

The Smith reference simply discusses combinations of G⁺ (more commonly known as ganciclovir) with various other antivirals. Smith notes in column 11, lines 6-13, that the amounts of ganciclovir and the other drugs used in the combinations are appropriate for *in vitro* testing to show synergy, but that the amounts used *in vivo* should be those amounts of each drug known to be efficacious. Smith provides no *in vivo* results.

In fact, there are very few drug synergies that exist when combinations are used to treat human patients, the combination of sulfonamide and trimethotrim being one. In large part, the synergies seen *in vitro* or in animal models are exaggerated due to the limitations of the *in vitro* or animal model systems as discussed above. But practitioners were aware that it was rare that a purported synergy observed *in vitro* or in an animal model system was also present in humans.

In conclusion, one skilled in the art would **not have been motivated nor had any reasonable expectation of success** in combining an antiviral and a glucocorticoid for treatment of recurrent dermal herpes infections.

Appl. No. 10/771,259

The undersigned hereby declares that all statements made herein based upon knowledge are true, and that all statements made based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

DATED: 3 JULY 05
Dr. Spotswood Spruance

CURRICULUM VITAE

Spotswood Lee Spruance, M.D.

December 13, 2004/IND

DATE OF BIRTH: May 13, 1940
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SOCIAL SECURITY #: 001-30-9736
MARITAL STATUS: Joanne Weiherer, 1967
CHILDREN: Catherine Lee, 1973
Peter Spotswood, 1976

EDUCATION:

B.A., Harvard College, 1962.

M.D., Case-Western Reserve University School of Medicine, 1966.

Internship in Medicine, Cornell Service, Bellevue and Memorial Hospitals, New York City, New York, 1966-67.

Residency in Medicine, Cornell Service, Bellevue and Memorial Hospitals, New York City, New York, 1967-68.

Fellow in Infectious Diseases, Division of Infectious Diseases, University of Utah College of Medicine, Salt Lake City, Utah, 1970-72.

Visiting Scientist, Centre Internationale de Recherches Dermatologiques, Valbonne, France, 1986-87 (sabbatical year).

BOARD CERTIFICATION:

Internal Medicine, 1974

Infectious Diseases, 1974

MEDICAL LICENSURE:

Utah, 1970 (#0416110017, 70-151237-1205)

HONORS AND OTHER SCIENTIFIC RECOGNITION

Governor's Medal for Science and Technology (Utah, 1998)

Fellow, American Academy of Microbiology (January 23, 2001)

MILITARY SERVICE:

Epidemiology Intelligence Service Officer, National Center for Disease Control, USPHS, 1968-70.

PROFESSIONAL POSITIONS:

Medical Staff, University of Utah Hospital and Clinics, 1972-present.

Assistant Professor of Medicine, Division of Infectious Diseases, University of Utah College of Medicine, Salt Lake City, Utah, 1972-1978.

Associate Professor of Medicine, Division of Infectious Diseases, University of Utah School of Medicine, Salt Lake City, Utah, 1978-1985.

Professor of Medicine, Division of Infectious Diseases, University of Utah School of Medicine, Salt Lake City, Utah, 1985-present.

Associate Professor of Medicine, Division of Dermatology, University of Utah School of Medicine, Salt Lake City, Utah, 1982-1985.

Professor of Medicine, Division of Dermatology, University of Utah School of Medicine, Salt Lake City, Utah, 1985-95.

Adjunct Professor of Dermatology, Department of Dermatology, University of Utah School of Medicine, 1996-present.

Adjunct Associate Professor of Pharmaceutics, College of Pharmacy, University of Utah, Salt Lake City, Utah, 1984-1986.

Adjunct Professor of Pharmaceutics and Pharmaceutical Chemistry, College of Pharmacy, University of Utah, Salt Lake City, Utah, 1986-present.

Director, University of Utah Health Sciences AIDS Center, 1992-1995.

Medical Preceptor, Sexually Transmitted Diseases Clinic, Salt Lake City-County Health Department, 1995-2003.

Director, Center for Clinical Studies, University of Utah Health Sciences Center, 1996-1999.

VISITING PROFESSORSHIPS:

Visiting Professor, Department of Medical Microbiology and Infectious Diseases and the Faculty of Dentistry, University of Alberta, Edmonton, Canada, September 26-28, 1988.

Visiting Professor, Department of Medicine, University of British Columbia, Vancouver, B.C., Canada, January 21-23, 1986.

SITE VISITS, REVIEW COMMITTEES AND CONSULTATIONS FOR THE NATIONAL INSTITUTES OF HEALTH:

Site visit team, National Institute of Dental Research (NIDR), University of Michigan Dental Institute, 1977 and 1978. Institute renewal application, Subject: Viral diseases of the oral cavity.

Site visit team, National Institute of Allergy and Infectious Diseases (NIAID) University of Colorado Department of Dermatology, 1980. Asthma and Allergic Disease Center proposal: "Immune Mechanisms of Allergic Skin Disorders". Subject: Relationship between herpes simplex and erythema multiforme.

Invited consultant for goals and objectives, NIDR, 1980.

Site Visit Team, NIDR, University of Pennsylvania Dental School, 1981. General Clinical Research Center Application. Subject: Development and clinical testing of a herpes simplex virus vaccine.

Site Visit Team, NIAID, University of Rochester School of Medicine, 1982. Clinical Research Center renewal application.

Site Visit Team, NIDR, Santa Barbara, CA, 1984. Small Business Innovation Research Grant. Title: "Preclinical Studies of the Algal Antiherpetic Rhodophycin".

NIH Special Study Section, Small Business Innovative Research Grants. Washington, D.C., December 11, 1984.

NIH Ad Hoc Technical Review Group. Critique of proposals in response to RFP NIH-NIAID(MIDP)-NCI-86-10 entitled "Establishment of AIDS Treatment Evaluation Units". Washington, D. C., February 25-26, 1986.

NIH Special Review Committee. Critique of proposals in response to RFP NIH-NIAID-DMID-91-02 entitled "Animal Models of Human Virus Infection for Evaluation of Experimental Therapeutics". Washington, D.C., July 23-25, 1990.

NIH Special Review Committee. Critique of proposals in response to RFPs NIH-DAIDS-91-09/10 entitled "Evaluation of AIDS Therapies in Animal Retroviral Models" and "Evaluation of Pharmacokinetics of AIDS Therapies in Non-Human Primates". Washington, D.C., February 24-25, 1991.

Data and Safety Monitoring Board, NIAID. Clinical trials of therapies for herpes zoster and herpes simplex virus encephalitis, 1991-1996.

Ad Hoc Review Committee. Program Project application entitled "Clinical epidemiology and pathogenesis of asymptomatic herpes simplex virus infection." Teleconference, February 24, 1994.

Data and Safety Monitoring Board, NIAID. A phase I/II multi-center, randomized, double-blind, vehicle-controlled study to assess safety and preliminary efficacy of R-848 in preventing ultraviolet-radiation-induced reactivation of herpes labialis, 1998-2000.

Data and Safety Monitoring Board, NIAID. Valtrex in the treatment of herpes encephalitis, 1999-present.

NIH Ad Hoc Technical Review Group. Critique of proposals in response to RFP NIH-NIAID entitled "AIDS Treatment Evaluation Units". Washington, D. C., September 9-11, 2001.

EDITORIAL POSITIONS:

Editorial Board, *Skin Pharmacology*, 1989-1997.

Editorial Board, *Antimicrobial Agents and Chemotherapy*, 1992-1995.

Section Editor (Antiviral Agents), *Antimicrobial Agents and Chemotherapy*, 1995-present.

Editorial Board, *Antiviral Research*, 1999-present.

MANUSCRIPT REFEREE:

Annals of Internal Medicine

Archives of Internal Medicine

Journal of Infectious Diseases

Antiviral Research

Antimicrobial Agents and Chemotherapy

Journal of the American Medical Association

Clinical Infectious Diseases

INDUSTRY APPOINTMENTS:

Board of Directors, Research Industries Corporation, 1985-1991.

Advisory Panel on Infectious Disease Therapy, the United States Pharmacopeial Convention, 1990-1995.

Advisory Board on Herpes Vaccines, SmithKline Beecham, 1995-present.

Scientific Advisory Board, Virotex Corporation, 1993-1998.

R&D Executive Committee, Associated Regional and University Pathologists Institute, 1996-present

Ad hoc consultant: GlaxoWellcome, Research Industries, Bristol-Myers Squibb, SmithKline Beecham, Shaman, Lidak, 3M, Menarini, Drug Innovation and Design, Medivir, Bayer, Warner-Lambert, Panacea, Xavos, Viropharma, Nika, Atrix, Ancile, Ventana

INTRAMURAL ADMINISTRATIVE EXPERIENCE:

Chairman, Ambulatory Care Committee, 1972-79.

Chairman, Clinical Faculty Committee, 1973-81.

Chairman, Tenured Faculty Review Appeals Committee, 1981-83.

Preclinical Promotions Committee, 1982-1986.

Steering Committee, University of Utah Hospital Information Systems, 1991-93.

Chairman, Steering Committee, Health Sciences AIDS Center, 1992-96.

Information Management Advisory Group, University of Utah Health Sciences Center, 1994-96.

University of Utah Biosafety Committee, 1996-1999.

University of Utah Institutional Review Board, 1999-2002.

INTRAMURAL TEACHING EXPERIENCE:

Freshman Physical Diagnosis, 1972-75.

Medical Ward Attending, 1972-present.

Infectious Diseases Consultation Attending, 1972-present.

Infectious Diseases Clinic Attending, 1994-1998

Medical Microbiology Course, School of Medicine:

Director, Bacteriology Section, 1975.

Director, Parasitology Section, 1977-85.

Coursemaster, 1982-85.

Faculty, 1975-1992; 1998-2002.

PROFESSIONAL SOCIETIES:

Fellow, American College of Physicians
Salt Lake County Medical Society
Utah State Medical Association
American Federation for Clinical Research
American Society of Microbiology #1238120
Western Society for Clinical Research
Infectious Diseases Society
International Society for Antiviral Research
Western Association of Physicians

PUBLICATIONS:

A. Original Articles

1. Spruance SL and Smith CB: Joint complications associated with derivatives of HPV-77 rubella vaccine. *Am J Dis Child* 122:105-109, 1971.
2. Kahn JB, Spruance SL, Harbottle J, Cannon P and Schultz MG: Echinococcosis in Utah. *Am J Trop Med* 21:185-188, 1972.
3. Spruance SL, Klock LE Jr., Bailey A, Ward JR and Smith CB: Recurrent joint symptoms in children vaccinated with HPV-77 DK12 rubella vaccine. *J Pediatr* 80:413-417, 1972.
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5. Spruance SL, Smith CB, Krall J and Ward JR: Growth of Newcastle disease virus and rubella virus in rheumatoid and non-rheumatoid synovial cell cultures. *Infect Immun* 6:326-329, 1972.
6. Spruance SL and Bailey A: Colorado tick fever: A review of 115 laboratory confirmed cases. *Arch Intern Med* 131:288-293, 1973.
7. Klock LE Jr., Spruance SL, Andersen FL, Juranek DD and Kagan IG: Detection of asymptomatic hydatid disease by a community screening program. *Am J Epidemiol* 97:16-21, 1973.
8. Spruance SL: Latent period of 53 years in case of hydatid cyst disease. *Arch Intern Med* 134:741, 1974.
9. Kagan IG, Klock LE Jr. and Spruance SL: Studies on echinococcosis in North America. *El Torax* 23:3-8, 1974.
10. French RS, Ziter FA, Spruance SL and Smith CB: Chronic meningitis due to *Propionibacterium acnes*. *Neurology* 24:624-628, 1974.
11. Spruance SL, Richards OC, Smith CB and Ward JR: DNA polymerase activity of cultured rheumatoid synovial cells. *Arthritis Rheum* 18:229-233, 1975.
12. Spruance SL, Metcalf R, Smith CB, Griffiths MM and Ward JR: Chronic arthropathy associated with rubella vaccination. *Arthritis Rheum* 20:741-747, 1977.
13. Spruance SL, Overall JC Jr., Kern ER, Krueger GG, Pliam V and Miller W: Natural history of recurrent herpes simplex labialis: Implications for antiviral therapy. *N Engl J Med* 297:69-75, 1977.
14. Griffiths MM, Spruance SL, Ogra PL, Thompson GR and DeWitt CS: Histocompatibility antigens and recurrent episodic arthropathy associated with rubella vaccination. *Arthritis Rheum* 20:1192-97, 1977.
15. Spruance SL, Wilcox B, Richards OC, Foster DN, Huseby RA and Samuels LT: DNA synthesis and DNA polymerase activity in Leydig cells of diethylstilbestrol-stimulated mouse testes. *Cancer Res* 38:424-430, 1978.
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18. Spruance SL, Krueger GG, MacCalman J, Overall JC Jr. and Klauber MR: Treatment of recurrent herpes simplex labialis with levamisole. *Antimicrob Agents Chemo* 15:662-665, 1979.

19. Green JA, Spruance SL and Cheson BD: Favorable outcome of central nervous system toxoplasmosis occurring in a patient with untreated Hodgkin's disease. *Cancer* 45:808-810, 1980.
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21. Spruance SL, Ashton BN and Smith CB: Preparation and characterization of high-specific activity radiolabeled 50 S measles virus RNA. *J Virological Meth* 1:223-228, 1980.
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23. Overall JC Jr., Spruance SL and Green JA: Interferon in herpes simplex labialis vesicle fluid. *J Inf Dis* 143:543-547, 1981.
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25. Guinan ME, MacCalman J, Kern ER, Overall JC Jr. and Spruance SL: Recurrent symptomatic genital herpes simplex. Clinical and virologic course in 27 women. *N Engl J Med* 304:759-764, 1981.
26. Whitley RJ, Soong S-J, Hirsch MS, Karchmer AW, Dolin R, Galasso G, Dunnick JK, Alford CA and the NIAID Collaborative Antiviral Study Group (SL Spruance): Herpes simplex encephalitis. Vidarabine therapy and diagnostic problems. *N Engl J Med* 304:313-318, 1981.
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29. Spruance SL, Green JA, Chiu G, Yeh T-J, Wenerstrom G and Overall JC Jr.: Pathogenesis of herpes simplex labialis. II. Correlation of vesicle fluid interferon with lesion age and virus titer. *Infection Immunity* 36:907-910, 1982.
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33. Green JA, Weiss FN and Spruance SL: Spontaneous and induced interferon production by peripheral blood mononuclear leucocytes from humans with herpes labialis. *J Immunol* 131:2827-2829, 1983.
34. Spruance SL, McKeough MB and Cardinal JR: Penetration of Guinea Pig Skin by Acyclovir in Different Vehicles and Correlation with the Efficacy of Topical Therapy of Experimental Cutaneous Herpes Simplex Virus Infection. *Antimicrobial Agents and Chemotherapy* 25:10-15, 1984.
35. Cheson BD, Samlowski WE, Tang TT and Spruance SL: Value of open lung biopsy in 87 immunocompromised patients with pulmonary infiltrates. *Cancer* 55:453-459, 1984.
36. Spruance SL, Crumpacker CS, Schnipper LE, Kern ER, Marlow S, Arndt KA and Overall JC Jr.: Early, patient-initiated treatment of herpes labialis with topical 10% acyclovir. *Antimicrobial Agents and Chemotherapy* 25:553-555, 1984.
37. Spruance SL: Pathogenesis of herpes simplex labialis: Excretion of virus in the oral cavity. *J Clin Micro* 19:675-679, 1984.
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40. Spruance SL, McKeough MB, Sugibayashi K, Robertson F, Gaede P, Clark DS: Effect of azone and propylene glycol on the skin penetration of trifluorothymidine and the efficacy of different topical formulations against cutaneous herpes simplex virus infection in guinea pigs. *Antimicrobial Agents and Chemotherapy* 26:819-823, 1984.
41. Freeman DJ, Sacks SL, Ashe MA, De Clercq E and Spruance SL: Preclinical assessment of topical treatments for herpes

- simplex virus infection: 5% (E) -5-(2-bromovinyl)-2'-deoxyuridine (BVDU) cream. *Antiviral Research* 5:169-177, 1984.
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 46. Spruance SL, Freeman DJ and Sheth NV: Comparison of topically applied 5-ethyl-2'-deoxyuridine and acyclovir in the treatment of cutaneous herpes simplex virus infection in guinea pigs. *Antimicrobial Agents Chemother* 28:103-106, 1985.
 47. Freeman DJ, Wenerstrom G and Spruance SL: Treatment of recurrent herpes simplex labialis with topical butylated hydroxytoluene. *Clinical Pharmacology and Therapeutics* 38:56-59, 1985.
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 49. Holak EJ, Wu J and Spruance SL: Value of serum arabinitol for the management of Candida infections in clinical practice. *Mycopathologia* 93:99-104, 1986.
 50. Sheth NV, Freeman DJ, William IH and Spruance SL: The influence of Azone, propylene glycol and polyethylene glycol on in vitro skin penetration of trifluorothymidine. *International J Pharm* 28:201-209, 1986.
 51. Freeman DJ and Spruance SL: Prediction of the efficacy of topical herpes simplex virus treatments from an index of in vitro drug characteristics. *J Infectious Dis* 153:64-70, 1986.
 52. Douglas JM Jr., Judson FN, Levin MJ, Spruance SL, Bosso J, Johnston JM, Corey L, McMillan JA and Wiener LB: A multicenter placebo-controlled trial of topical 8% arildone cream in early recurrent genital herpes. *Antimicrobial Agents and Chemotherapy* 29:464-467, 1986.
 53. Freeman DJ, Sheth NV and Spruance SL: Failure of topical acyclovir in ointment to penetrate human skin. *Antimicrobial Agents and Chemotherapy* 29:730-732, 1986.
 54. Spruance SL, Freeman DJ and Sheth NV: Comparison of foscarnet cream, acyclovir cream and acyclovir ointment in the topical treatment of experimental cutaneous herpes simplex virus type 1 infection. *Antimicrobial Agents and Chemotherapy* 30:196-198, 1986.
 55. Green JA and Spruance SL: Induced regional differences in cutaneous cell-mediated immunity in the mouse. *Int Archs Allergy Appl Immun* 81:31-34, 1986.
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70. JD Kriesel, IP Hwang, SL Spruance, DJ Carr UV Exposure and hyperthermia affect transcription factors in the trigeminal ganglion. International Herpes Virus Workshop, York, England, August, 1998.
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73. McKeough M and Spruance S. Denavir, Zovirax Cream and Zovirax Ointment in the topical treatment of experimental dorsal cutaneous herpes simplex virus type 1 infection in the guinea pig. 11th International Conf on Antiviral Research (International Society for Antiviral Research), San Diego, CA, April 5-10, 1999 (Abstract 134).
74. McKeough MB and Spruance SL. Combination of peroral famciclovir and a topical corticosteroid for the treatment of experimental ultraviolet radiation-induced herpes labialis: A double-blind, placebo-controlled trial. 39th Interscience Conf on Antimicrobial Agents and Chemotherapy, San Francisco, September 26-29, 1999 (Abstract 1408, pg. 432).
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76. Spruance S, Stanberry LR, Cunningham AL, Mindel A, Scott LL, Aoki FY, Lacey CJ, Dubin G and Slaoui M. Gender-specific efficacy of a prophylactic SBAS4-adjuvanted gd2 subunit vaccine against genital herpes disease: results of two clinical efficacy trials. 40th Interscience Conf on Antimicrobial Agents and Chemotherapy, San Francisco, Toronto, September 17-20, 2000. Program Addendum, "Late Breaker" Abstract L-6.
77. Spruance SL, Johnson J, Spaulding T and ACV Cream Study Group. Acyclovir cream for the treatment of herpes simplex labialis: the results of two double-blind, placebo-controlled trials. 14th International Conference on Antiviral Research, Seattle, Washington, April 8-12, 2001.
78. McKeough, M, Amin AN, Douglas M and Spruance S. Fusaric acid and acyclovir ointment in the topical treatment of experimental dorsal cutaneous herpes simplex virus type 1 infection in the guinea pig. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 22-25, 2001.
79. Spruance S, Cunningham A, Stanberry L and Dubin G for the GlaxoSmithKline Biologicals Vaccine Efficacy Study Group. Transmission of herpes simplex virus infection within monogamous relationships: a prospective study of 1171 couples. 39th Annual Meeting of the Infectious Diseases Society of America, San Francisco, California, October 25-28, 2001.
80. John D. Kriesel, Brandt B. Jones, S.L. Spruance. Mechanism of HSV reactivation: effects of explantation on cell signaling proteins in trigeminal ganglion neurons. International Herpes Virus Workshop, Regensburg, Bavaria, Germany, August, 2001.
81. John D. Kriesel, Brandt B. Jones, S.L. Spruance. The Roles of Inflammation, STAT Transcription Factors, and Nerve Growth Factor in Viral Reactivation and Herpes Keratitis. Oral presentation at the Molecular Pathogenesis of Infectious and Inflammatory Eye Research Conference, Oklahoma City, October, 2001.

82. McKeough M, Amin A, Douglas M and Spruance S. Fusaric acid combined with acyclovir and acyclovir ointment in the topical treatment of experimental dorsal cutaneous herpes simplex virus 1 (HSV-1) infection in the guinea pig. 15th International Conf on Antiviral Research (International Society for Antiviral Research), Prague, Czech Republic, March 17-21, 2002 (Abstract 68)
83. Spruance SL, Jones TM, Blatter MM, Vargas-Cortes M, Barber J, Goldstein D, and Schultz M. Oral valaciclovir for the treatment of herpes labialis: two trials of early, high-dose, short-course therapy. 15th International Conf on Antiviral Research (International Society for Antiviral Research), Prague, Czech Republic, March 17-21, 2002
84. John Kriesel, Brith Otterud, Andreas Peiffer, Brandt Jones, S.L. Spruance, Mark Leppert. The Genetic Basis of Susceptibility to Herpes Simplex Labialis in Humans. Late-breaker oral presentation at the 40th Annual Meeting of the Infectious Disease Society of America, Chicago, Illinois, October 27, 2002.
85. McKeough MB and Spruance SL. Abreva vs acyclovir in 80% DMSO in the treatment of experimental dorsal cutaneous herpes simplex virus type 1 infection in the hairless guinea pig. Antiviral Research 2003;57:A67 (Abstract 90).
86. JD Kriesel, BB Jones, SL Spruance. Antiviral Activity of Triplex-Forming Oligonucleotides Against HSV-1. Poster presentation at the International Society for Antiviral Research meeting, April 2003, Charleston, South Carolina.
87. John Kriesel, Brith Otterud, Brandt Jones, S.L. Spruance, Mark Leppert. The Genetic Basis of Susceptibility to Herpes Simplex Labialis in Humans. International Herpesvirus Workshop, Madison, Wisconsin, July 2003.
88. John D. Kriesel, Andrea White, Frederick G. Hayden, S.L. Spruance, and Jack Petajan. Multiple Sclerosis Attacks are Associated with Picornavirus Infections. Infectious Disease Society of America, San Diego, California, October 2003.

INVITED LECTURES:

1. "Pharmacologic aspects of topical antiviral therapy". Genital Herpes Workshop, NIAID, May 12-13, 1981.
2. "Treatment of oro-labial herpes simplex with acyclovir". International ACV Symposium, NIAID, September 9-11, 1981.
3. "Labial herpes infection: Natural course and study design". VIII International Congress of Infectious and Parasitic Diseases, Stockholm, Sweden, June 7-11, 1982.
4. "Novel Antiviral Agents". College of Clinical Pharmacy, Kansas City, Missouri, June 26, 1982.
5. "DMSO as a Vehicle for Topical Antiviral Chemotherapy". Conference on the Biological Actions and Medical Applications of DMSO, New York Academy of Sciences, New York City, September 15-17, 1982.
6. "Development of an Effective Treatment for Herpes Simplex Labialis". 13th International Congress of Chemotherapy, Vienna, Austria, August 28 - September 2, 1983.
7. "Treatment of Orofacial Herpes Infections". Symposium on Pharmacological and Clinical Approaches to Herpesviruses and Virus Chemotherapy, Oiso, Japan, September 10-13, 1984.
8. "Clinical Overview of Cutaneous HSV Infections" and "Correlations Between Efficacy and in vitro Drug Characteristics." Workshop on Evaluation of Antiviral Drugs in Animal Models, NIAID, May 16-17, 1985.
9. "Prediction of the Clinical Efficacy of Antiviral Agents from Experimental Studies". Pfizer, Inc., Groton, Connecticut, May 9, 1986.
10. "Prophylactic Therapy with Oral Acyclovir (ACV) for Ultraviolet (UV) Light-Induced Herpes Simplex Labialis." Wellcome International Antiviral Symposium, Monte Carlo, Monaco, December 2-4, 1987.
11. "Herpes simplex virus type 1: Incidence and changing patterns of infection." American Academy of Family Practice, New Orleans, LA, October 3-6, 1988.
12. "The pathogenesis of recurrent herpes simplex: Is this an immunopathologic disease?" Fourth Annual Review of Infectious Diseases for the Specialist, University of Colorado Health Sciences Center, Denver, CO, October 6, 1988.
13. "Antiviral chemotherapy of herpes simplex labialis: History and future prospects." The Squibb Institute for Medical Research, Princeton, NJ, February 5, 1989.
14. "Treatment of ultraviolet radiation-induced herpes simplex labialis with peroral and topical acyclovir." Burroughs Wellcome Co., Research Triangle Park, NC, December 15, 1989.
15. "Clinical aspects of infection with herpes simplex virus" and "Viral pneumonias in adults." Infectious Diseases Symposium, Mercy General Hosp., Sacramento, CA, Feb 1-2, 1991.

16. "Pathogenesis and treatment of HSV-1." Third Triennial Symposium on New Directions in Antiviral Chemotherapy. University of California San Francisco, San Francisco, CA. November 14-16, 1991.
17. "Short term suppression of herpes labialis." Herpes - a Global Challenge (Burroughs Wellcome Symposium). Berlin, June 3-6, 1992.
18. "Mucocutaneous herpes simplex virus and varicella zoster virus infections: Diagnosis and treatment." Grand Rounds, University of Wisconsin-Madison Medical School, Madison, WI, February 19, 1993.
19. "Treatment of mucocutaneous herpesvirus infections." Grand Rounds, Veterans Affairs Medical Center, Roanoke, Virginia, May 4, 1993.
20. "A controlled trial comparing continued zidovudine with didanosine in HIV infection." State-of-the-art Conference on Antiretroviral Therapy for HIV Infected Patients. National Institutes of Health, Washington, DC, June 22-25, 1993.
21. "Herpes simplex labialis." Update '94: Clinical Management of Herpesviruses (University of British Columbia). Whistler, Vancouver, January 30-February 1, 1994.
22. "The pathogenesis and treatment of herpesvirus infections." Grand Rounds, Mount Zion Medical Center, San Francisco, CA, June 17, 1994.
23. "STD's other than AIDS." Update in Internal Medicine: Primary Care for the Internist (University of Utah School of Medicine), Park City, Utah, July 9-14, 1995.
24. "Management of herpes simplex labialis." 3rd International Symposium on Cutaneous Fungal, Bacterial and Viral Infection and Therapy (University of California San Francisco, San Francisco, CA), San Francisco, CA, September 14-17, 1995.
25. "Imiquimod cream for the treatment of genital and perianal warts." 3rd International Symposium on Cutaneous Fungal, Bacterial and Viral Infection and Therapy (University of California San Francisco, San Francisco, CA), San Francisco, CA, September 14-17, 1995.
26. "Initial use of anti-HIV therapy". Clinical Care of the AIDS Patient (University of California San Francisco, San Francisco, CA), Sun Valley, Idaho, August 1-6, 1996.
27. "Correlation between the dermal pharmacokinetics of topically administered antiviral compounds and efficacy against cutaneous herpes simplex virus infections". Workshop on Bioequivalence of Topical Dermatologic Dosage Forms - Methods of Bioequivalence, American Association of Pharmaceutical Scientists, Washington, DC, September 4-6, 1996.
28. "The nature and origin of resistance to recurrent oral-facial HSV-1 disease". Infectious Diseases Seminar, University of Rochester School of Medicine, Rochester, N.Y., September 9, 1996.
29. "Antiretroviral drugs: Pharmacology, Toxicology, Interactions and Resistance". Clinical Care of the AIDS Patient (University of California San Francisco, San Francisco, CA), San Francisco, CA, December 5-7, 1996.
30. "Anti-HIV therapy: Toxicity and drug interactions". Clinical Care of the AIDS Patient (University of California San Francisco, San Francisco, CA), Sun Valley, Idaho, August 21-26, 1997.
31. "What's new in wart therapy?: Treatment of external genital warts with topical imiquimod (Aldara)". Fall Meeting of the Intermountain Dermatology Society (University of Utah), Sun Valley, Idaho, September 19-20, 1997.
32. "Antiretroviral drugs: Pharmacology, Toxicology, Interactions and Resistance". Clinical Care of the AIDS Patient (University of California San Francisco, San Francisco, CA), San Francisco, CA, December 4-6, 1997.
33. "Herpes labialis: Over, under and behind the counter - where are we?" Update '98: Clinical Management of Viral Infections (University of Vancouver, British Columbia), Whistler, B.C., Canada, February 7-10, 1998.
34. "HIV: Predicting Drug Interactions". Update '98: Clinical Management of Viral Infections (University of Vancouver, British Columbia), Whistler, B.C., Canada, February 7-10, 1998.
35. "Diagnosis and therapy of herpes simplex virus infections". Infectious Diseases in Clinical Practice (University of California San Francisco and the University of Utah), Park City, Utah, February 22-27, 1998.
36. "Viral load testing and HIV therapy". Infectious Diseases in Clinical Practice (University of California San Francisco and the University of Utah), Park City, Utah, February 22-27, 1998.
37. "Drugs and drug interactions in HIV therapy". Clinical Care of the AIDS Patient (University of California San Francisco, San Francisco, CA), Sun Valley, Idaho, August 6-11, 1998.
38. "Common drug toxicities". Clinical Care of the AIDS Patient (University of California San Francisco, San Francisco, CA), Sun Valley, Idaho, July 29 - August 3, 1999

39. "The primary immune response and recurrences of herpes simplex". 9th International Conference on Immunobiology and Prophylaxis of Human Herpesvirus Infections (University of Chicago), Ciocco, Castelvechio Pascoli-Lucca, Italy, October 9-11, 1999.
40. "Drug toxicities". Clinical Care of the AIDS Patient (University of California San Francisco, San Francisco, CA), San Francisco, CA, December 2-4, 1999.
41. "Managing genital warts: The new approach to drug therapy and vaccines". Update 2000: Clinical Management of Viral Infections (University of Vancouver, British Columbia), Whistler, B.C., Canada, February 5-8, 2000.
42. "Advances in the treatment of herpetic viral infections." Advances in Internal Medicine (University of Utah School of Medicine), Park City, Utah, February 8-12, 2000
43. "Common drug toxicities in HIV medicine". Clinical Care of the AIDS Patient (University of California San Francisco, San Francisco, CA), Sun Valley, Idaho, August 3-8, 2000
44. "Managing the Adverse Effects of Antiretroviral Therapy". The Medical Management of AIDS: A Comprehensive Review of HIV Management (University of California San Francisco), San Francisco, California, December 7-9, 2000
45. "Herpes Simplex Infections". 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 22-25, 2001
46. "Herpes Simplex Virus Vaccines." 40th Annual Meeting of the Association of Reproductive Health Professionals, La Jolla, CA, September 10-13, 2003.
47. "HIV and HSV". Virology: A New Perspective (University of Sidney Westmead), Sidney, Australia, March 5-6, 2004.

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